Atherosclerosis 275 (2018) 225–231

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

# Peak lung function during young adulthood and future long-term blood pressure variability: The Coronary Artery Risk Development in Young Adults (CARDIA) study

Yacob G. Tedla [a, *], Yuichiro Yano [b], Bharat Thyagarajan [c], Ravi Kalhan [d], Anthony J. Viera [e, f], Sharon Rosenberg [d], Philip Greenland [g], Mercedes R. Carnethon [g]

[a] Center for Health Information Partnership, Feinberg School of Medicine, Northwestern University, USA
[b] University of Mississippi Medical Center, University of Mississippi, USA
[c] Department of Laboratory Medicine and Pathology, School of Medicine, University of Minnesota, USA
[d] Pulmonary and Critical Care Medicine, Feinberg School of Medicine, Northwestern University, USA
[e] Department of Epidemiology, University of North Carolina at Chapel Hill, USA
[f] Department of Family Medicine, University of North Carolina at Chapel Hill, USA
[g] Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, USA

ARTICLE INFO

*Article history:*
Received 24 April 2018
Received in revised form
5 June 2018
Accepted 13 June 2018
Available online 15 June 2018

*Keywords:*
Long-term blood pressure variability
Visit-to-visit blood
Pressure variability
Lung function

ABSTRACT

*Background and aims:* Long-term blood pressure variability (BPV) is associated with cardiovascular events independent of mean blood pressure (BP); however, little is known about its predictors.
*Methods:* Using data from the CARDIA study, we investigated the association between peak lung-function and long-term BPV in 2917 individuals (mean age 24.8 years, 45.3% males, 58.6% whites) who were not taking antihypertensive medications. Lung-function was measured using forced vital capacity (FVC) and forced expiratory volume in 1-s (FEV1) at years 0, 2, 5, 10 and 20 and the maximum score attained was considered as peak lung-function. Variability independent of the mean (VIM) and coefficient of variation (CV) of BP were calculated to quantify BPV since achieving peak lung-function across 9 visits over 30 years.
*Results:* In a multivariate linear regression models, individuals in the 2nd (−0.64 mmHg; 95% CI: −1.06, −0.19), 3rd (−0.96; −1.47, −0.45), and 4th (−0.85: −1.53, −0.17) quartiles of FVC had lower VIM of systolic BP than the those in quartile 1 ($p$-trend = 0.005). CV of systolic BP was also lower by −0.58 (−0.98, −0.19), −0.92 (−1.42, −0.43), and −0.74 (−1.40, −0.08) percentage points, in the three progressively higher quartiles of FVC compared to quartile 1 ($p$-trend = 0.008). Similar findings were observed when the outcome was diastolic BPV. There was no association of FEV1 and FEV1-to-FVC ratio with BPV.
*Conclusions:* These findings suggest that smaller lung volume or restrictive lung disease during young adulthood, which result in lower peak FVC, may independently increase the risk of higher long-term BPV during middle adulthood.

Published by Elsevier B.V.

## 1. Introduction

Long-term blood pressure (BP) variability refers to fluctuations in BP that occur over weeks, months, and years [1]. Long-term BP variability has been recently identified as an independent risk factor for the development and progression of vascular events [1–4]. Higher long-term BP variability was shown to correlate with progression of subclinical outcomes such as carotid intima-media thickness [5], aortic and carotid stiffness [6], and micro-albuminuria [7] independent of mean BP. In addition,

*Abbreviations:* BP, blood pressure; CV, coefficient of variation; FEV1, forced expiratory volume in the first 1 s; FVC, forced vital capacity; GFR, glomerular filtration rate; HDL, high density lipoprotein; VIM, variability independent of the mean.

* Corresponding author. Center for Health Information Partnership, Feinberg School of Medicine, Northwestern University, 625 N Michigan Avenue Office 15, Chicago, IL, 60611, USA.
*E-mail address:* yacob.tedla@northwestern.edu (Y.G. Tedla).

https://doi.org/10.1016/j.atherosclerosis.2018.06.816
0021-9150/Published by Elsevier B.V.

independent of mean BP, long term variability in BP was associated with development of coronary heart disease, heart failure, cardiovascular mortality [8], stroke [9], chronic kidney disease [3], and cognitive function [4]. Although arterial stiffness [6], poor BP control [10], and noncompliance to medications [10] have been suggested as potential predictors of long-term BP variability, little is known about other factors that may predict long-term BP variability.

Lower lung function was associated independently with CVD and all-cause mortality [11,12] and these associations have been observed even among individuals without evident respiratory symptoms [13]. Lower lung function is believed to contribute to CVD events partly by increasing the risk of hypertension [14,15]. In addition to independently predicting mean BP and future incident hypertension [14,15], lower lung function may also be a risk factor for higher long-term BP variability. In fact, lower lung function was associated with a decrease in central vascular elasticity [16]. This may in turn play a role at increasing long-term BP variability because lower aortic distensibility was independently associated with higher long-term BP variability [6]. The objective of this study was to investigate the association of peak lung function with long-term variability in systolic and diastolic BPs.

## 2. Materials and methods

### 2.1. Study design and participants

The Coronary Artery Risk Development in Young Adults (CARDIA) study is a longitudinal population based study with an aim of investigating factors that influence the development of cardiovascular diseases (CVD) in young adults [17]. Participants were 5115 blacks and whites and men and women aged 18–30 years at baseline (Year 0, 1985 to 1986) and were recruited from 4 centers across the United States (Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California). The study protocol was approved by the institutional review board at all 4 field centers and all participants consented to participate in the study. Participants were recruited by random-digit dialing from total communities or specific census tracts in Chicago, Birmingham, and Minneapolis [17]. In Oakland, participants were randomly selected from the Kaiser Permanente Medical Care Program (KPMCP) [17]. KPMCP is the largest not-for-profit, integrated health care delivery system in the United States [18]. Further information about the KPMCP can be found in McCarthy et al. [18] Fifty percent of the invited participants were enrolled and formed the CARDIA cohort. Eight follow-up examinations were conducted during 1987–1988 (Year 2), 1990–1991 (Year 5), 1992–1993 (Year 7), 1995–1996 (Year 10), 2000–2001 (Year 15), 2005–2006 (Year 20), 2010–2011 (Year 25), and 2015–2016 (Year 30). Details on design and objectives of CARDIA can be found in Friedman et al. [17].

Participants were eligible for the present analysis if they: (i) had at least 3 B P measurements since achieving peak lung function because $\geq$3 values are required to calculate indices of BP variability [19] and (ii) were not on antihypertensive medications at all the visits because BP medication can mask pathophysiologic variations in BP [10]. Participants who met eligibility and had complete data on adjusted covariates and peak lung function were 2833 for FVC and 2917 for FEV1 and were included in our analyses.

### 2.2. Peak lung function

Lung function was measured at year 0 (baseline) and follow-up years 2, 5, 10 and 20 usingforced vital capacity (FVC) - the amount of air that can be maximally and forcibly expelled from the lungs after a maximal inhalation and forced expiratory volume in 1-s (FEV1) - the volume of air that can be forcibly exhaled in 1 s after full inspiration [20]. Following the American Thoracic Society recommendations [21–24], lung function was measured with the participants standing using Collins Survey 8-L water sealed spirometer and an Eagle II Microprocessor (Warren E. Collins, Inc, Braintree, MA) at years 0, 2, 5, and 10 and using dry rolling seal OMI spirometer (Viasys Corp, Loma Linda, CA) at year 20. A comparability study between the Collins Survey and OMI spirometers was performed on 25 volunteers and there was consistency between the readings with an average difference of 6 mL for FVC and 21 mL for FEV1 [14,25]. To minimize methodological error, daily assessment for leaks, volume calibration with a 3-L syringe, and weekly calibration in the 4- to 7-L range were performed on the testing machines. The largest value of FEV1 and FVC were obtained from five technically satisfactory maneuvers, and the difference between the two largest reading of the FEV1 and FVC were within 150 mL in almost all cases. Peak FVC and FEV1 were defined as the maximum score of FVC and FEV1, respectively, attained during years 0, 2, 5, 10 and 20.

### 2.3. Long-term blood pressure variability

At each examination, brachial BP was measured on the right arm while in a seated position after participants were seated for 5 min in a quiet room. Trained and certified research staff took three measurements of BP, each separated by 1 min, and the average of the second and third readings was used in the analysis. Hawksley random zero sphygmomanometer (WA Baum Company, Copiague, NY) was used to measure BP from baseline to year 15 examination, and an automated oscillometric BP monitor (Omron HEM-907XL; Online Fitness, Santa Monica, CA) was used at examination years 20–30. A calibration study was performed, and year 20–30 B P values were standardized to the sphygmomanometric measures [14].

Two indices were used to quantify long-term systolic and diastolic BP variability since achieving peak lung function: within-individual coefficient of variation (CV - ratio of standard deviation to the mean) and variability independent of mean (VIM) of BP. VIM was calculated as the $SD^{*}(M/x)^{P}$ where SD is standard deviation of within-individual BP measurements, M is average value of BP in the cohort, and x is within-individual mean BP since attaining peak lung function. $p$ is the regression coefficient on the basis of regressing natural logarithm of SD on natural logarithm of the multiplication of M and x [26]. VIM was shown to correlate highly with other indices of BP variability [27] while its correlation with mean BP level is almost zero [9,28]. In our study, the correlation of VIM with CV was 0.97 for systolic and 0.99 for diastole BP while its correlation with mean was 0.01 for both systolic and diastolic BPs. VIM allows assessing the association of risk factor with BP variability while removing the confounding effect of mean BP level.

Demographic, anthropometric, behavioral factors, laboratory data, and history of chronic diseases for the present study were obtained from baseline and were measured following standard procedures. See Supplemental Data 1 for detailed description of the measurement of adjusted covariates.

### 2.4. Statistical analysis

The association between peak lung function and long-term BP variability was evaluated using linear regression model while adjusting for potential confounders. We drew *a priori* directed acyclic graph [29] and applied Pearl's back-door criterion [30] using DAGitty [31] to identify potential confounders (see Supplemental Data 2). Age, sex, race, education, pack-years of cigarette smoking, physical activity, alcohol intake, height, BMI, hypercholesterolemia,